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Regioselective silylation of 5-(2′-hydroxyethyl)cyclopent-2-en-1-ol and 6-(2′-hydroxyethyl)cyclohex-2-en-1-ol

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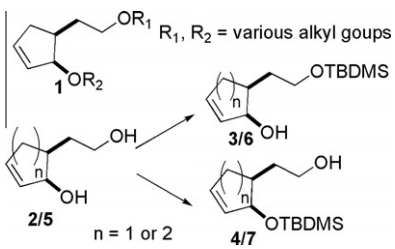
ABSTRACT

Herein we report regioselective and mild reactions for the *tert*-butyldimethylsilyl mono-protection of 5-(2′-hydroxyethyl)cyclopent-2-en-1-ol (**2**) and 6-(2′-hydroxyethyl)cycohex-2-en-1-ol (**5**) at the primary hydroxyl group or at the secondary allylic hydroxyl group. The different steric environment surrounding the secondary allylic and saturated primary alcohols is mainly invoked to rationalize the observed regioselectivity.

One of the most common hydroxyl group protecting methods in synthetic organic chemistry is the formation of various types of silyl ethers.[1] Among the many trialkylsilyl reagents, *tert*-butyldimethylsilyl chloride (TBDMSCl) has become the most common since it was introduced by Corey[2] in 1972. Silyl ethers are usually prepared by the treatment of alcohols with the corresponding silyl chloride in the presence of stoichiometric amounts of bases such as imidazole, 4-dimethylaminopyridine (DMAP), and triethylamine.[1,2] Additionally, the silylation under acidic conditions has also been reported. Allysilyl and silyl enol ethers silylate alcohols under the influence of a catalytic amount of *p*-toluenesulfonic acid,[3,4] iodine,[5] trifluoromethanesulfonic acid,[6] and Lewis acid $Sc(OTf)_3$.[7] Further, a simple method for the silylation of alcohols in DMSO–hexane without a base and catalyst was reported by Oriyama and co-workers.[8]

We have previously prepared one family of compounds **1** (Scheme 1), as conformationally restricted insect pheromone mimics.[9,10] During the synthesis of **1**, the key step is the regioselective silylation of diol **2** to give protected products **3** (primary OH silylation) or **4** (secondary allylic OH silylation) (Scheme 1), depending on the reaction conditions. We have examined this reaction, and optimal selectivity toward primary OH silylation is achieved by treating diol **2/5** with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of a base and catalyst (Scheme 1). Optimal selectivity toward secondary allylic OH silylation is obtained with TBDMSCl in the absence of base and catalyst. Examples are known of the selective silylation of a primary alcohol group over a saturated secondary alcohol.[11,12] However, for our substrate **2/5**, the primary and secondary allylic alcohol groups are differentiated, depending on the reaction conditions. Herein, we disclose selective reactions in the silylation of **2/5** under different conditions that give either mostly **3/6** or mostly **4/7**. A reaction mechanism for the regioselectivity is also proposed.

The selective silylation of the primary alcohol group of **2** (Table 1, entries 1–5) was achieved under several conditions, namely, with triethylamine (TEA), dimethylaminopyridine (DMAP), imidazole or pyridine as a base and CH_2Cl_2 as the solvent. Under those conditions, the less hindered and more reactive primary alcohol group of **2** was selectively silylated. Presumably, the reaction follows a classic nucleophilic catalytic process[13,14] in which the first step in silylating an alcohol is a pre-equilibrium between the silylating reagent and a nucleophile activator such as DMAP or imidazole. The subsequent nucleophilic attack of the activated species by the alcohol yields the silyl ether.



Scheme 1. Regioselective silylation of diol **2/5** to give silyl ethers **3/6** and **4/7.**

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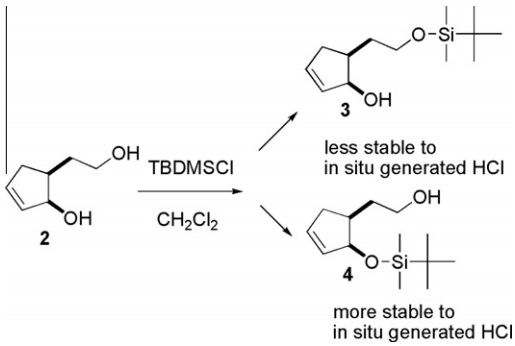
Table 1
Ratio of product **3** and **4** under various conditions

Entry	Conditions base (equiv)[a,b]	Ratio of **3**–**4** (**3**/**4**)[c]
1	TEA (1.2 equiv)	96/4
2	DMAP (1.2 equiv)	100% **3**
3	TEA (1.2 equiv), DMAP (0.1 equiv)	100% **3**
4	Imidazole (1.2 equiv), DMAP (0.1 equiv)	100% **3**
5	Pyr. (1.2 equiv)	99/1
6	$NaHCO_3$ (1.2 equiv)	8/92
7	Na_2CO_3 (1.2 equiv)	10/90
8	NaOAc (1.2 equiv)	100% **4**
9	Without base and catalyst	100% **4**

[a] All treatments have TBDMSCl in 1.2 equiv.
[b] All reactions were carried out in CH_2Cl_2, at rt, for 12 h.
[c] The product ratio was determined by GC.



Scheme 2. Products formed during silylation of **2** in the absence of a base and catalyst.

Table 3
The solvent effect of silylation of **2** under non-basic conditions

Entry	Solvent log*P*	Solvents	Isolated yield of **4** (%)
1	−1.22	DMSO	63
2	−1.04	DMF	32
3	−0.15	MeCN	13
4	0.53	THF	28
5	0.68	AcOEt	18
6	1.25	CH_2Cl_2	35
7	3.6	Hexane	23

While examples are also known for the selective silylation of a secondary allylic alcohol in the presence of a saturated secondary alcohol, the majority of cases involve sterically hindered or geometrically biased substrates in which the allylic alcohol undergoes preferential silylation due to steric accessibility. In our case, the more hindered allylic alcohol was selectively silylated (Table 1, entries 6–9). Remarkably, for entry 9, the silylated allylic alcohol product **4** was obtained exclusively. It seems that the less reactive and more hindered alcohol was silylated preferentially. However, based on TLC and GC analysis, both products **3** and **4** were formed in the initial stages of the reaction. Due to acidic reaction solutions for entries 6–9, with HCl generated in situ as the silylation by-product and no base available for neutralization (entry 9), the less stable product **3** was hydrolyzed and the more stable product **4** survived (Table 2 and Scheme 2). In those cases in which the base was a solid that did not dissolve in the reaction solvent (entries 6–8), product **4** also formed predominantly. Furthermore, when equimolar amounts of **3** and **4** were treated with 1 drop of 1 M HCl in dichloromethane solution, 35% of **3** and 66% of **4** were left for 20 h. This result also suggested that **4** is more stable than **3** under acidic conditions. To mimic in situ generated conditions, 1–2 drops of concentrated HCl were added to a CH_2Cl_2 solution of **3**, giving an approximate concentration of the HCl generated in the silylation process. The mixture was stirred at room temperature. Compound **3** was hydrolyzed within 5 min.

Furthermore, the solvent effects for the silylation of diol **2** were also examined. The results are summarized in Table 3. When the reaction was carried out in dimethyl sulfoxide (DMSO), the product **4** was obtained in a 63% isolated yield. When other solvent systems such as DMF, MeCN, THF, AcOEt, CH_2Cl_2, and hexane were used, the corresponding silyl ether **4** was obtained in relatively lower yields. These observations are consistent with results reported by Oriyama and co-workers.[8] As suggested in their report, presumably the trialkylsilyl chloride was more strongly activated by DMSO through the coordination of the DMSO oxygen atom to the silicon atom, leading to a higher yield in DMSO. Similarly, spontaneous aldol and Michael reactions of enoxytrimethylsilanes can take place in good yields in dipolar aprotic solvents such as DMSO.[15]

Three hypotheses were considered to account for the selective formation of products **3** and **4** under non-basic conditions. The first hypothesis focused on the differences in acidities between allylic and saturated primary alcohols. Generally, the pK_a values of alcohols that are adjacent to an unsaturated system are lower than those of the corresponding saturated alcohols.[16] This is due to the increased electronegativity of the unsaturated functionalities.[16] The increased acidity of the allylic alcohol could potentially facilitate hydrogen bonding to the base, leading to the increased nucleophilicity of allylic relative to the saturated alcohol. However, when **1** was treated with various organic bases (see Table 1, entries 1–5), product **3** was formed preferentially. In the absence of base, products **3** and **4** were formed nonpreferentially at the beginning of the reaction (see Table 2). Over time, product **3** disappeared and product **4** became the sole product (Table 2). From those results, it seemed that the difference of acidities of two alcohols did not play a significant role for the observed regioselectivity.

The second hypothesis focused on the differences in the steric environments surrounding the secondary allylic and saturated primary alcohols. In the presence of base and catalyst, the less hindered primary alcohol was silylated preferentially to give product **3**. In contrast, the more hindered product **4** survived in situ generated HCl in the absence of base. Those results were well consistent with the second hypothesis that selective silylation comes from the

Table 2
Product distribution during silylation of **2** in the absence of base[a]

Time (min)	Ratio of **3** and **4** (**3**/**4**)[b]
5	41/59
15	38/62
30	16/84
60	0.5/99.5
90	100% **4**
120	100% **4**
1080	100% **4**

[a] Reactions were carried out in CH_2Cl_2 at room temperature.
[b] The product distribution was determined by GC.

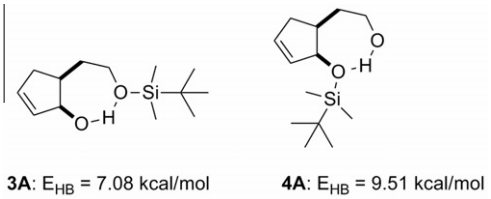


Figure 1. Hydrogen bonding species of **3** and **4**.

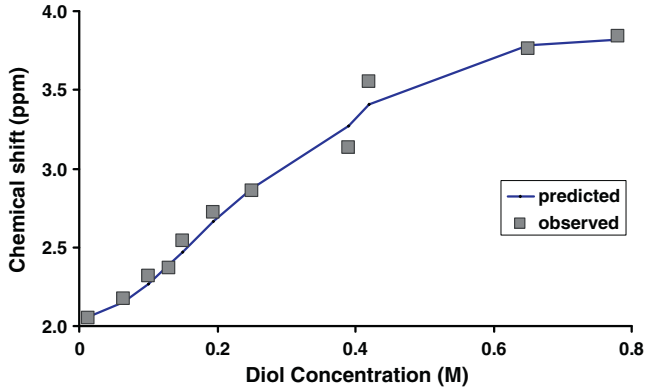
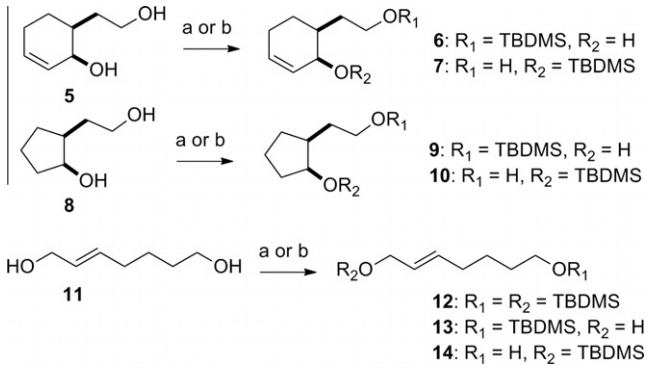


Figure 2. Hydrogen bonding experiment of **2** in $CDCl_3$. Predicted values were obtained by fitting the data to a two-step cooperative binding model (see Supplementary data for details): step 1 $K_a = 7.6 \times 10^{-2}$ M, Hill coefficient = 2.0; step 2 $K_a = 3.8 \times 10^{-3}$ M, Hill coefficient = 5.1. K_a = association equilibrium constant.



Scheme 3. Products formed during silylation of **5**, **8** and **11** with or without base and catalyst: (a) TEA (1.2 equiv), DMAP (0.1 equiv), TBDMSCl (1.2 equiv), CH_2Cl_2; (b) TBDMSCl (1.2 equiv), CH_2Cl_2.

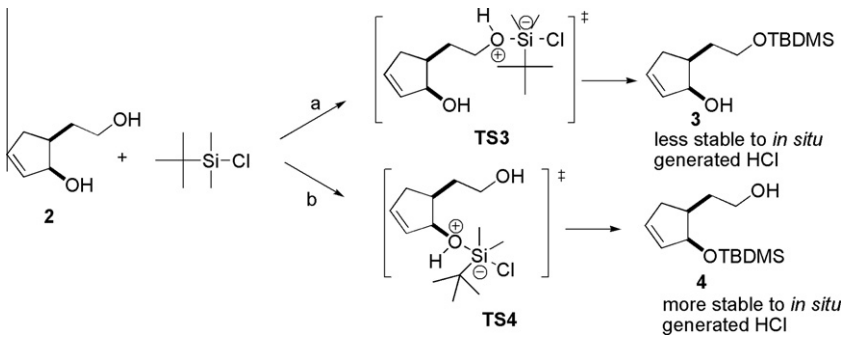
fact the secondary allylic alcohol is more sterically demanding than the saturated primary alcohol.

The third hypothesis was that the selectivity could be derived from an intramolecular hydrogen bonding network in the molecules **3** and **4** (Fig. 1). Based on DFT calculations using Gaussian (see Supplementary data section 2 for details), molecules **3** and **4** can form strong hydrogen bonding species such as 3A and 4A, with hydrogen bonding energies of 7.08 kcal/mol and 9.51 kcal/mol, respectively. As mentioned previously, both products **3** and **4** were formed in the initial stages of the reaction in the absence of base and catalyst. However, with in situ generated HCl, product **3** was hydrolyzed and product **4** survived. The calculated stronger hydrogen bonding energy of **4A** is 1.43 kcal/mol stronger than that of **3A**, leading to stronger stability of **4** than that of **3**. This result is well consistent with our experimental observations.

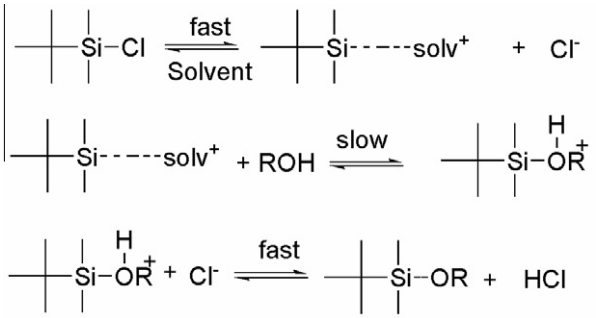
To investigate the further probability that the diol might also form H-bonded dimers in solution, the chemical shift dependence of the OH protons was investigated in $CDCl_3$ (see Supplementary data section 4). The results suggest that a weak H-bonded dimer forms in two steps (Fig. 2). Both steps are weak binding and with some positive cooperativity. The first step displays slightly stronger binding but weaker cooperativity than the second step. This suggests that initial dimerization with the first H-bond is less cooperative but stronger than the second H-bond formation. The kinetics of dissociation and association of the diol dimer also was studied by NMR experiments (see Supplementary data section 4). The dissociation and association of the diol dimer reach equilibrium in seconds, suggesting that dissociation and association are fast processes.

In order to investigate if the observed regioselectivity can be applied to other diol systems. Diols **5**,[9,17] **8**, and **11**[18] were synthesized according to reported methods (Scheme 3). For six-membered system **5**, the reaction behavior was similar to the five-membered system **2**. When **5** was treated with DMAP and TEA, product **6** was formed selectively. Product **7** was obtained in the absence of base and catalyst. For the saturated five-membered ring system **8**, with or without base and catalyst, the primary alcohol silylated product **9** was generated exclusively. The result was also well consistent with that fact the primary alcohol is less hindered than the secondary alcohol. Finally, for an open chain system such as **11**, with similar steric environments for both allylic and saturated alcohols, two alcohols were silylated with base and catalyst in a ratio of 1:1:2 for products **12**, **13**, **14** (see Supplementary data section 1). The more acidic allylic alcohol was silylated to give **14** in a moderate selectivity. Without base or catalyst, a ratio of 0.2:1:1.5 for products **12**, **13**, **14** (see Supplementary data section 1) was obtained.

Presumably, the reaction without base and catalyst proceeds as a nucleophilic attack upon the silicon atom of the silyl donor, affording bimolecular transition states **TS3** and **TS4** (Scheme 4). After the repulsion of Cl^-, they give silyl-oxonium ions. The consequent deprotonation of the oxonium ion by Cl^- gives rise to HCl. However, further investigation of the kinetics of the silylation reaction in CH_2Cl_2, in the absence of base (see Supplementary data section 3), revealed that the reaction is of less than first order ($\leqslant 1$) in TBDMSCl and greater than first order (>1) in diol. The low dependence of the rate on TBDMSCl concentration suggests a mechanism (Scheme 5): the TBDMSCl first dissociates into a silyl-solvent cation complex and Cl^-. The cation complex is then attacked by the alcohol moiety, giving a silyl-oxonium ion. The consequent deprotonation of the oxonium ion by Cl^- gives rise to HCl. In fact, the observation of complexes of silyl cations with solvent molecules



Scheme 4. A putative mechanism (S_N2-like) of silylation of diol **2** in the absence of a base and nucleophilic catalyst.



Scheme 5. A putative mechanism (S_N1-like) of silylation of diol **2** in the absence of a base and nucleophilic catalyst.

involving some degree of covalent bonding has been documented.[19] Therefore, both of the two mechanistic pathways might exist in our reaction. Namely, both a bimolecular mechanism (S_N2-like) and a S_N1-like mechanism are operating during the reaction process. In the absence of base, the HCl either accumulates in the solvent or evaporates. In those cases where no base was added, the HCl caused the 1° silyl ether to back-react, but the 2° allylic silyl ether withstood the HCl and accumulated.

In conclusion, the selective silylation of **2** and **5** proceeds with high selectivity for substrates in which the secondary allylic and saturated primary alcohols are sterically different. There are two potential sites for silylation, the primary $-CH_2OH$ and secondary alcohol giving products **3/6** and **4/7**, respectively. Under various conditions, both sites are observed to be silylated, and in the absence of base or catalyst, only the secondary site is silylated. In the presence of in situ generated HCl, the primary silyl product is unstable, leaving only the secondary one as an observed product. Our proposed mechanism starts with the nucleophilic attack of alcohol with TBDMSCl to form a bimolecular transition sate, followed by the repulsion of Cl^- and deprotonation. In the absence of base, HCl forms, and this causes the desilylation of the 1° silyl ether. The 2° allylic silyl ether forms more slowly, but is more stable toward the HCl formed in the reaction. Therefore, in the presence of base the kinetic (1°) product predominates whereas in the absence of base the thermodynamic (2° allylic) product predominates.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data (^1H, ^{13}C NMR, IR, MS); molecular optimization using Gaussian calculations; kinetic data; and the NMR study for dimerization of **2**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.020.

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